

**REMARKS AND ARGUMENTS**

**Amendments to the Claims**

Claims 46-49, 51-52, and 64-67 are currently pending in the application. Claims 1-45, 50, 53-63 have been canceled without prejudice to future filing. Claims 46, 51, 64, and 65 are currently amended. Claim 46 is amended to more clearly recite the subject matter considered to be the invention by reciting antagonists selected from soluble 4-1BB proteins, antibodies that bind 4-1BB and antibodies that bind 4-1BBL. Basis for this amendment is found in the specification, for example pages 17 and 18 of the specification, as well as in the claims as originally filed. Claims 51, 64 and 65 are amended to depend from claim 46. Therefore, the basis for the amendments to the claims is found in the specification and does not represent new matter. Entry of the amendments to the claims is respectfully requested.

**Rejections on the Basis of 35 U.S.C. § 112**

Claims 46-52 and 63-67 are rejected on the basis of 35 U.S.C. §112, first paragraph as allegedly lacking enablement in the specification for reciting “preventing cardiotoxicity”. This rejection is respectfully traversed. The Examiner has stated that the data provided in the instant specification allegedly does not support “preventing” and specifically that the mouse data in the instant specification showing lack of mortality or lack of signs of severe cardiotoxicity does not support “preventing” cardiotoxicity because some cardiotoxicity may have been present. Applicants do not agree, and submit that the specification does indeed enable the method of claim 46 since the specification does describe how to administer 4-1BB antagonists to prevent cardiotoxicity, for example, pages 55-64. However, in order to expedite prosecution of the application, claim 46 has been amended to remove “preventing” cardiotoxicity from the claim. Therefore, based on the amendment to claim 46, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 46-52 and 63 to 67 on the basis of 35 U.S.C. §112, first paragraph, enablement.

Claims 46-49 and 52 remain rejected on the basis of 35 U.S.C. § 112, first paragraph, as allegedly lacking written description in the specification. This rejection is respectfully traversed.

While not agreeing with the Examiner's arguments (page 4 of the Office Action), in order to expedite the prosecution of this application, claim 46 has now been amended to incorporate the limitations of claim 50. Soluble 4-1BB proteins, antibodies against 4-1BB and antibodies against 4-1BBL are clearly described in the specification, for example, pages 17-18 of the specification, as well as Table 5, pages 86 and 87. Therefore, on the basis of the amendment to claim 46 and the arguments presented above, Applicants respectfully request reconsideration of the rejection of claims 46-49 and 52 on the basis of 35 U.S.C. §112, first paragraph, written description.

**Rejections under 35 U.S.C. § 103(a)**

Claims 46-52 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. published application 2004/0028687 to Waelti, in view of U.S. Patent 5,674,704 to Goodwin et al. This rejection is respectfully traversed.

35 U.S.C. § 103(a) states that "A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

For all of the reasons set forth in the previous Response and Amendment of March 18, 2009, and the Response of May 14, 2008, Applicants maintain that the subject matter of claims 46-49, and 51-52 would not have been obvious to a person having ordinary skill in the art at the time the invention was made in view of the three references cited by the Examiner. Applicants maintain again that Yndestad et al. actually teaches away from selection of 4-1BB as the target to antagonize, since upregulation of 4-1BBL in peripheral blood mononuclear cells could not be confirmed using RT-PCR, and receptors for 4-BBL were not known to be expressed in the heart (page 180 of Yndestad et al.). Furthermore, none of the patients screened in Yndestad et al.

suffered from chronic heart failure induced by treatment with chemotherapeutic agents such as doxorubicin.

Further, Applicants question the use of the reference to Waelti to allegedly show that doxorubicin can result in cardiotoxicity often resulting in cardiomyopathy with serious congestive heart failure. Applicants note that US application 2004/0028687 to Waelti was published February 12, 2004, after the filing date of the provisional applications to which the instant application claims priority (the instant application serial number 10/646,308 claims priority to provisional application serial number 60/406,418, filed August 28, 2002, and provisional application serial number 60/494,457, filed August 12, 2003). Therefore, the paragraph relied on in Waelti (00220) was not publicly available to one of ordinary skill in the art at the time of the invention. Further, it is clear that Waelti does not describe the basic inventive concept of the instantly pending claims (Waelti describes synthetic membrane vesicles for delivery of therapeutic substances), and was only relied on for a few sentences in paragraph 0022, which amounts to background information in that reference. Therefore, the reference to Waelti as a whole does not teach or suggest the claimed subject matter.

Applicants therefore maintain that the claimed subject matter could not have been obvious at the time of the invention to one of ordinary skill in the art based on these three references, in particular since Waelti et al. was not yet published. Finally, Applicants maintain that the Examiner has not provided any motivation to combine these references in the manner done by the Examiner. These references have no apparent relationship to each other, and Waelti et al. was not even published at the time of the invention. Applicants maintain that the combination of references was only selected in hindsight as provided by the instant application, which is not a proper basis for an obviousness rejection.

Therefore, based on the amendments to the claims, and the arguments presented above, as well as the arguments previously presented in the Response of March 18, 2009, and the Response of May 14, 2008, Applicants request reconsideration and withdrawal of the rejection of claims 46-52 on the basis of 35 U.S.C. §103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. application 2004/0028687 to Waelti, in view of U.S. Patent 5,674,704 to Goodwin et al.

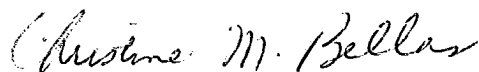
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**CONCLUSION**

Applicants maintain that the claims as amended are in form for allowance. Applicant's attorney invites the Examiner to call her at the number given below if it would be helpful in advancing the prosecution of this application.

Respectfully submitted,



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